

Blunted as well as exaggerated cardiovascular reactivity to stress is associated with negative health outcomes

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Blunted as well as exaggerated cardiovascular reactivity to stress is associated with negative health outcomes

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Cardiovascular reactivity and health

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Abstract: The reactivity hypothesis implicates exaggerated cardiovascular reactions to acute psychological stress in the development of hypertension and other cardiovascular disease outcomes. However, exaggerated cardiovascular reactivity has also been suggested as a mediator between a variety of psychosocial and behavioural risk factors and cardiovascular disease. Recent data analyses from the West of Scotland Twenty-07 study and our own group are discussed together, to show that blunted as well as exaggerated cardiovascular reactivity to stress may be associated with negative health outcomes. Blood pressure and heart rate were assessed at rest and during an acute mental arithmetic stress task. We show that depression and obesity are associated with blunted rather than exaggerated reactivity. These seemingly paradoxical results are discussed in terms of implications for the reactivity hypothesis.

Key words: cardiovascular reactivity, depression, obesity,

The reactivity hypothesis, as originally conceptualised, proposed that large magnitude cardiovascular reactions to acute psychological stress exposures increase the risk of the development of hypertension (Obrist, 1981). Most prospective studies to date have tested what might be referred to as a main effects model (Carroll, Smith, Shipley, Steptoe, Brunner & Marmot, 2001), i.e., that high reactivity to stress *per se* is pathogenic. Such studies have measured cardiovascular reactivity to a variety of acute laboratory-based stress tasks such as mental arithmetic under time pressure, cold pressor, memory tasks, mirror tracing and others (see, Allen, Matthews, & Sherman, 1997; Carroll, Ring, Hunt, Ford, & Macintyre, 2003; Carroll, Smith, Sheffield, Shipley, & Marmot, 1995; Carroll, et al., 2001; Everson, Kaplan, Goldberg, & Salonen, 1996; Everson, Lynch, Chesney, Kaplan, Goldberg, Shade, Cohen, Salonen & Salonen, 1997; Hassellund, Flaa, Sandvik, Kjeldsen & Rostrup, 2010; Kamarck, Everson, Kaplan, Manuck, Jennings, Salonen, & Salonen, 1997; Lynch, Everson, Kaplan, Salonen, & Salonen, 1998; Markovitz, Raczynski, Wallace, Chettur, & Chesney, 1998; Matthews, Woodall, & Allen, 1993; Matthews, Zhu, Tucker, & Whooley, 2006; Treiber, Turner, Davis, & Strong, 1997). All of which are shown to elicit considerable heart rate and/or blood pressure reactions via beta- and/or alpha-adrenergic stimulation.

Collectively, such studies indicate that high magnitude haemodynamic reactions to stress confer a modest but reasonably consistent risk for developing high blood pressure (Carroll, et al., 2003; Carroll, et al., 1995; Carroll, et al., 2001; Chida & Steptoe, 2010; Everson, et al., 1996; Markovitz, Matthews, Kannel, Cobb, & D'Agostino, 1993; Markovitz, et al., 1998; Matthews, et al., 1993; Treiber, et al., 1997), carotid atherosclerosis (Everson, et al., 1997; Kamarck, et al., 1997; Heponiemi, Elovainio, Pulkki, Puttonen, Raitakari & Keltikangas-Jarvinen, 2007; Lynch, et al., 1998; Matthews, et al., 2006; Treiber, Kamarck, Schneiderman, Sheffield, Kapuku, & Taylor, 2003), and increasing left ventricular mass (al'Absi, Devereux, Rao, Kitzman, Oberman, Hopkins & Arnett, 2006; Allen, et al., 1997; Georgiades, Lemne, de Faire, Lindvall, & Fredrikson, 1997; Treiber et al., 2003). The most compelling evidence emerges from prospective studies, where an initial assessment of cardiovascular reactivity is followed by measurement of blood pressure status in the future. For example, in the Twenty-07 study in the West of Scotland, the magnitude of cardiovascular reactions to stress predicted 2-3% of the variance in 5-year upward drift in blood pressure, when controlling for initial resting blood pressure as well as body mass index (Carroll, et al., 2003). This has also been shown in a number of large scale studies in a range of populations (Carroll, et al., 2001; Markovitz, et al., 1998; Treiber, et al., 1997).

Recently, high cardiovascular reactivity has also been suggested as a mediator between a wide variety of psychosocial and behavioural risk factors and cardiovascular disease (Chida & Hamer, 2008), such as life events stress (Lepore, Miles, & Levy, 1997; Matthews, Gump, Block, & Allen, 1997), social support (O'Donovan & Hughes, 2008; Roy, Steptoe, & Kirschbaum, 1998), hostility (Suls & Wan, 1993; Vella & Friedman, 2009), and smoking (Davis & Matthews, 1990; Tersman, Collins, & Eneroth, 1991). The rarely articulated but implicit assumption is that low physiological reactivity in the face of acute psychological challenge is the more adaptive response, with no negative consequences for health or behaviour, i.e., low reactivity is benign or even protective. By extension, then, low reactivity would be expected to characterise more positive psychological and behavioural factors implicated in mitigating cardiovascular disease risk. This assumption has recently been subject to challenge (Carroll, Phillips, & Lovallo, 2009, in press). Analyses from the West of Scotland Twenty-07 study and from our own laboratory will be used to illustrate that caution is warranted when ignoring the potential implications of low reactivity. First indications that supposedly negative characteristics or behaviours might not always be associated with higher cardiovascular reactivity emerged from analyses of the associations between life events stress and reactivity in the Twenty-07 study data. For example, socio-economic status was positively associated with acute stress reactivity such that those from manual occupational households had lower cardiovascular responses to acute stress than those from non-manual households (Carroll, Harrison, Johnston, Ford, Hunt, Der, & West, 2000). Similarly, given that acute laboratory stress responses are considered to be indicative of how one responds to stressful events in real life, it was expected that those with higher stress ratings for events which had occurred over a two year period, would have greater cardiovascular responses to laboratory stress. However, data from the Twenty-07 study showed that middle-aged and older adults who rated their stressful experiences as more highly disruptive, at the time of occurrence and at the time of recall, exhibited blunted systolic blood pressure reactions to acute mental stress (Carroll, Phillips, Ring, Der, & Hunt, 2005). Likewise, among the younger adults in the Twenty-07 study, the total number of events and the number of personal events were negatively associated with systolic blood pressure and heart rate reactions to acute stress, whereas the number of work-related events was negatively associated with diastolic blood pressure and pulse rate reactivity (Phillips, Carroll, Ring, Sweeting, & West, 2005).

The present article will address the scope and the limitations of the reactivity hypothesis through discussion of both cross-sectional and prospective associations between cardiovascular reactivity to acute stress and two key psychosocial/behavioural risk factors; depression and obesity, in a large community-based sample.

Depression

Depression has been linked prospectively with mortality from cardiovascular disease (Hemingway & Marmot, 1999; Wulsin, Vaillant, & Wells, 1999). Specifically, depression appears to be a risk factor for future cardiovascular events following acute myocardial infarction (Frasure-Smith & Lesperance, 2003; Frasure-Smith, Lesperance, Gravel, Masson, Juneau, Talajic, & Bourassa, 2000; Lesperance, Frasure-Smith, Talajic, & Bourassa, 2002), although this has not been shown in all studies (Lane, Carroll, Ring, Beevers, & Lip, 2001). The mediators and mechanisms underlying this association have yet to be established, but might include factors such as socio-economic position; ill-health and disability; unhealthy behaviours (Wulsin, et al., 1999); increased platelet aggregation (Mikuni, Kagaya, Takahashi, & Meltzer, 1992); and exaggerated cardiovascular reactions to psychological stress exposure (Kibler & Ma, 2004). With regard to this latter possibility, depression has been associated with a number of alterations in autonomic function. For example, enhancement of cardiac sympathetic activity relative to vagal tone has been reported in those with depression and subclinical depressive symptoms (Carney, Rich, teVelde, Saini, Clark, & Freedland, 1988; Light, Kothandapani, & Allen, 1998), as have increased plasma noradrenalin concentrations in patients with major depression (Rudorfer, Ross, Linnoila, Sherer, & Potter, 1985). Thus, the hypothesis that such autonomic dysregulation in depression may also be manifest as exaggerated cardiovascular reactivity, which in turn increases the risk of cardiovascular pathology, is intuitively appealing. There would appear to be at least some provisional evidence that symptoms of depression may be associated with heightened reactivity. For example, in a study of 91 healthy participants, those with high amounts of depressive symptoms manifested significantly greater systemic vascular resistance in response to a stressor task than did those with low amounts of depressive symptoms (S. C. Matthews, Nelesen, & Dimsdale, 2005). A meta-analysis of 11 relevant studies found small to moderate effect sizes indicative of a positive relationship between depressive symptomatology and cardiovascular reactions to acute psychology stress (Kibler & Ma, 2004). Unfortunately, none of the aggregate effects were statistically significant at conventional levels. Previous studies generally tested fairly small samples and few adjusted for potential confounding variables such as demographic factors and medication status. In contrast, in a larger sample of over 100 coronary artery disease patients, higher depressive symptom scores were associated with lower, not higher, cardiovascular reactions to acute psychological stress, even after controlling for a number of likely confounders (York, Hassan, Li, Li, Fillingim, & Sheps, 2007). The West of Scotland Twenty-07 dataset was used to revisit this issue in a substantial and demographically diverse sample of participants (Carroll, Phillips, Hunt, & Der, 2007). Statistical

adjustment for a range of possible confounders was possible. Uniquely, it was also possible to examine prospectively the association between cardiovascular reactivity and symptoms of depression five years later.

Obesity

Obesity is a fast growing epidemic in Western countries (Hughes, Frontera, Roubenoff, Evans, & Singh, 2002; WHO, 1997). The adverse health consequences of this increase in adiposity are starting to become apparent. Obesity, defined in terms of a body mass index of 30 kg/m^2 or more, has been consistently linked to all-cause and especially cardiovascular disease mortality (Adams, Schatzkin, Harris, Kipnis, Mouw, Ballard-Barbash, Hollenbeck, & Leitzmann, 2006; Allison, Fontaine, Manson, Stevens, & VanItallie, 1999; Calle, Thun, Petrelli, Rodriguez, & Heath, 1999; Prospective Collaboration Study, 2009; Stevens, Cai, Pamuk, Williamson, Thun, & Wood, 1998). It is also associated with a range of cardiovascular and metabolic disease outcomes, such as type 2 diabetes (Ford, Williamson, & Liu, 1997; Resnick, Valsania, Halter, & Lin, 2000) and hypertension (Hirani, Zaninotto, & Primatesta, 2007; Mokdad, Ford, Bowman, Dietz, Vinicor, Bales, & Marks, 2003), as well as overall cardiovascular disease morbidity (Bogers, Bemelmans, Hoogenveen, Boshuizen, Woodward, Knekt, van Dam, Hu, Visscher, Menotti, Thorpe, Jamrozik, Calling, Strand, & Shipley, 2007; Wilson, D'Agostino, Sullivan, Parise, & Kannel, 2002). Abdominal adiposity has also been linked with psychological distress, and it has been argued that an increased vulnerability to stress in the abdominally obese may be manifest as physiological hyper-reactivity (Bjorntorp, 1991). The impact of stress on the neuroendocrine system is thought to promote abdominal fat deposition (Bjorntorp, 1996), and it has been suggested that obesity, and especially central adiposity, will be associated with exaggerated cardiovascular reactions to stress (Davis, Twamley, Hamilton, & Swan, 1999; Waldstein, Burns, Toth, & Poehlman, 1999). The question arises as to whether obesity and exaggerated cardiovascular reactivity to acute stress are positively related or whether they are independent risk factors for cardiovascular pathology. A few mainly small scale studies have attempted to address this issue. Systemic vascular resistance levels during mental stress were negatively correlated with body mass index in 20 young men, but positively associated with waist-hip ratio; no significant associations emerged for blood pressure or cardiac activity during stress (Jern, Bergbrant, Bjorntorp, & Hansson, 1992). From a study of 95 adolescents, the peak systolic blood pressure (SBP) reaction to mental stress was larger for participants in the upper tertile of waist-hip ratios, although neither cardiac nor resistance reactions were associated with abdominal adiposity (Barnes, Treiber, Davis, Kelley, & Strong, 1998). Waist circumference has been reported to be positively associated with heart rate (HR) and diastolic

blood pressure (DBP) reactivity in a sample of 22 older African American men, but these associations did not withstand correction for basal blood pressure and insulin levels (Waldstein, et al., 1999). In a contemporary study of 24 women with body mass indices $\geq 28 \text{ kg/m}^2$, those with abdominal obesity, i.e. high waist-hip ratios, had higher DBP and systemic resistance reactions, but lower HR reactions, to a speech task (Davis, et al., 1999). In the largest study to date, body mass index was not significantly related to cardiovascular reactivity in 225 middle-aged public servants, although waist-hip ratio, a measure of abdominal adiposity, was positively associated with diastolic reactivity; the greater the abdominal adiposity, the higher the reactivity (Stephoe & Wardle, 2005). In addition, it was expected that disturbances in cardiovascular reactivity may reflect autonomic dysfunction which in turn may contribute to the development of obesity and adiposity, yet the upward drift in body mass index and waist-hip ratio over a 3-year follow-up period was not associated with the earlier measures of cardiovascular reactivity (Stephoe & Wardle, 2005). In contrast, greater fatness was related to a blunted vasodilatation response to mental stress in 48 healthy young men (Hamer, Boutcher, & Boutcher, 2007).

It is difficult to draw firm confident conclusions from the results of these studies, particularly given that most samples were small and poorly representative of the general population, and few adjusted for potential confounding variables, including baseline cardiovascular levels. The most consistent result appears to be a positive association between systemic resistance reactivity, as reflected by DBP and/or total peripheral resistance, and abdominal adiposity, although not all studies report this. The West of Scotland Twenty-07 dataset was again exploited to explore the association between cardiovascular reactivity and adiposity, both cross-sectionally and prospectively (Carroll, Phillips, & Der, 2008).

The present article is a synthesis of the unexpected negative associations between depression, obesity, and cardiovascular reactivity to acute stress as conducted as part of the West of Scotland Twenty-07 study. The associations which emerged from these analyses are discussed in the light of extensions and interpretations of the reactivity hypothesis.

Method

Participants and Procedure

Participants were all from Glasgow and surrounding areas in Scotland, recruited to the West-of-Scotland Twenty-07 Study and have been followed up at regular intervals since the baseline survey in 1987 (Benzeval, Der, Ellaway, Hunt, Sweeting, West, & Macintyre, 2009; Macintyre, 1987). Three

narrow age cohorts (aged 15, 35, and 55 years at entry) were chosen so that age-specific effects on health could be estimated with greater precision than through using a sample of all ages of the same size. The sample was almost entirely Caucasian reflecting the West of Scotland population from which it was drawn (Ecob, 1987). At follow-up 3 in 1995/96, participants were tested during the day in their own homes in a quiet room by specially trained nurses. Cardiovascular reactions to a psychological stress task, the paced auditory serial arithmetic test, were measured (Carroll, et al., 2000; Carroll, et al., 2003), following numerous other assessments of factors such as depressive symptomatology, body mass index, waist and hip circumference, smoking and other unhealthy behaviours, resting blood pressure, and medication status, see below. Reactivity data were available for 1647 participants of whom 592 (36%) were 24-year olds, 624 (38%) were 44-year olds, and 431 (26%) were 63-year olds. There were 890 (54%) women and 757 (46%) men in the sample, with 47% from manual occupation households. Household occupational group data were not available for five participants. Of the sample, 593 (36%) were current smokers, and 338 (21%) used to smoke. Seventy-one (4.3%) participants were taking anti-depressant medication, and 142 (8.6%) had hypertension and were taking medication to lower blood pressure. Mean (SD) body mass index, calculated from measured height and weight was 26.7 (4.26) kg/m². With the exception of reactivity, all of the above assessments were repeated at follow-up 4, five years later in 2000/01, at which point data were available for nearly 1300 participants. The mean (SD) temporal lag between the two follow-ups was 5.5 (1.00) years. The study was approved by the appropriate Ethics committees and conforms to the ethical guidelines of the Declaration of Helsinki.

Measures

Household occupational group was classified as manual or non-manual from the occupation of the head of household (usually the man) at the third follow-up, using the Registrar General's Classification of Occupations (1980). At both the third and fourth follow-ups, depression was measured using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) which comprises 14 items, seven measuring depression and seven measuring anxiety. At the third and fourth follow-ups, HADS data were available for 1608 and 1245 participants, respectively. At both the third and fourth follow-ups, height, using the Leicester Height Measure stadiometer, and weight, using portable electronic scales (Soehnle, Nassau, Germany), were measured and body mass index computed. The standard criterion of ≥ 30 kg/m² was used to identify obesity. At the third and fourth follow-ups, BMI data were available for 1647 and 1272 participants, respectively.

Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were measured by an Omron (model 705CP) sphygmomanometer. Following the interview, (at least an hour), there was a formal 5-minute period of relaxed sitting, at the end of which a resting baseline reading of SBP, DBP, and HR was taken. Two further SBP, DBP, and HR readings were taken during the 3-minute stress task, the first initiated 20 seconds into the task (during the slower sequence of numbers), and the second initiated 110 seconds later (at the same point during the faster sequence). For all readings, the nurses ensured that the participant's elbow and forearm rested comfortably on a table at heart level. The two task readings were averaged and the resting baseline value subsequently subtracted from the resultant average task value to yield reactivity measures for SBP, DBP, and HR for each participant.

Stress task

Participants undertook an acute psychological stress task: the paced auditory serial addition test (PASAT), which has been shown in numerous studies to reliably perturb the cardiovascular system (Ring, Burns, & Carroll, 2002; Winzer, Ring, Carroll, Willemsen, Drayson, & Kendall, 1999) and to demonstrate good test-retest reliability (Willemsen, Ring, Carroll, Evans, Clow, & Hucklebridge, 1998). Participants were presented with a series of single digit numbers by audiotape and requested to add sequential number pairs while retaining the second of the pair in memory for addition to the next number presented, and so on throughout the series. The first sequence of 30 numbers was presented at a rate of one every four seconds, and the second sequence of 30 at one every two seconds. The correctness of answers was recorded as a measure of performance.

Statistical analysis

Multiple regression was used to analyse the cross-sectional associations between cardiovascular reactivity and depression, body mass index, and waist-hip ratio in models adjusting first for baseline cardiovascular levels, then fully adjusted models were tested with covariates of reactivity, cohort, sex, household occupational group, performance score on the PASAT, and anti-hypertensive medication. For the sake of brevity and comparison, only fully adjusted associations are reported in the present article. Full unadjusted associations can be found in the initial reports of these associations (Carroll, et al., 2008; Carroll, et al., 2007; Phillips, Hunt, Der, & Carroll, 2010). The relationships between cardiovascular reactivity and obesity were tested using analysis of covariance (ANCOVA) with adjustment for potential confounding variables. Prospective analyses examining the association between reactivity and subsequent depression were by linear regression, and for the associations with subsequent obesity, by logistic regression. In all prospective linear and logistic regression analyses,

models were tested which, in effect, examined the change in the independent variable over time by entering the independent variable at follow-up 3 as a covariate, to provide a more stringent test of association.

Results

Reactivity

Two-way (baseline \times task) repeated measures ANOVAs indicated that the PASAT successfully increased cardiovascular activity overall for: SBP, $F(1,1646) = 1562.32, p < .001, \eta^2_p = .487$, for DBP, $F(1,1646) = 1066.62, p < .001, \eta^2_p = .393$, and for HR, $F(1,1646) = 1132.96, p < .001, \eta^2_p = .408$. SBP, DBP, and HR. Table 1 shows reactivity by age cohort, sex, and occupational group.

[Insert Table 1 about here]

Depression and cardiovascular reactivity

The mean depression score was 3.65 (SD = 2.86). The older two cohorts recorded higher depression scores than the youngest cohort, $F(2,1591) = 14.61, p < .001, \eta^2 = .018$; women displayed higher scores than men, $F(1,1591) = 7.63, p = .006, \eta^2 = .005$; those from manual occupational households had higher scores than those from non-manual households, $F(1,1591) = 7.10, p = .008, \eta^2 = .004$. Following adjustment for covariates as described above (baseline cardiovascular level, age cohort, gender, household occupational group, PASAT performance score and antihypertensive medication), and for body mass index, significant negative associations were observed between depression and reactivity: the higher the depression score, the lower the reactivity, for both SBP, $\beta = -.06, t = 2.53, \Delta R^2 = .004, p = .01$, and HR, $\beta = -.05, t = 2.00, \Delta R^2 = .002, p = .04$. As 71 (4%) of the sample reported taking antidepressants, this variable was additionally adjusted for, but the negative associations between depressive symptomatology and cardiovascular reactivity were not attenuated. The fully adjusted associations between depressive symptom score, using the cut-off of ≥ 8 to indicate possible caseness, and SBP and HR reactivity are displayed in Figure 1 as an illustration of the nature of these associations.

Recently, a novel prospective analysis was run in which depression score at follow-up 4 was entered as the dependent variable and depression score at follow-up 3 as a covariate. This enabled examination of the associations between reactivity and change in depression score over time. In these analyses, neither SBP nor DBP reactivity were related to HADS depression score five years later. However, HR

reactivity was again negatively associated with depression symptomatology, $\beta = -.05$, $t = 2.05$, $p = .04$, $\Delta R^2 = .002$, such that those with lower reactivity were more likely to display an increased depression score at the fourth follow-up.

Body mass index, obesity, and cardiovascular reactivity

At the earlier follow-up the younger cohort had lower body mass indices than the other two cohorts. Body mass index did not differ significantly between the sexes or between occupational class groups. Two hundred and twenty five (14%) of the participants met the criterion for obesity. Proportionally less of the younger cohort were identified as obese, $\chi^2(2) = 12.45$, $p = .002$. The frequency of obesity did not vary significantly by sex or occupational class. but participants who were taking blood pressure lowering medication (9%) had greater body mass indices than those not taking medication, $F(1,1640) = 20.02$, $p < .001$, $\eta^2_p = .012$. Current smokers had significantly lower body mass indices than ex- or never smokers, $F(2,1640) = 25.35$, $p < .001$, $\eta^2_p = .030$. Consequently, smoking was added to the range of covariates in analyses of reactivity and obesity.

In the fully-adjusted analyses, there was a significant negative association between body mass index and HR reactivity, $\beta = -.15$, $t = 6.25$, $p < .001$, $\Delta R^2 = .020$. Obese participants also exhibited much smaller HR reactions to stress than their non-obese counterparts, $F(1,1627) = 16.71$, $p < .001$, $\eta^2_p = .010$. Finally, given the associations with depression described above, we have since adjusted for depression status as well as the previous covariates, and the associations described above remained highly statistically significant. The fully adjusted association between obesity and HR reactivity is shown in Figure 1 as an illustration of the nature of the relationship.

As might be expected, body mass index significantly increased across the five years between follow-ups, $F(1,1272) = 342.12$, $p < .001$, $\eta^2_p = .212$, and at the later follow-up, a higher proportion, 261 (21%), of participants met the criterion for obesity. Reactivity did not predict the rise in either body mass index in the five years between the third and fourth follow-ups. However, in fully adjusted analyses with obesity at the fourth follow-up as the dependent variable and obesity at the third follow-up as a covariate, lower HR reactivity was associated with an increased risk of becoming obese over the five years between follow-ups, OR (95%CI) = 0.98 (0.96 – 0.99), $p = .008$.

[Insert Figure 1 about here]

Discussion

Depression

In these data, higher depressive symptom scores were associated with lower HR reactivity. What is especially compelling about these negative associations is that they were still evident following adjustment for a relatively comprehensive range of covariates. As indicated, a similar study examined the depression and reactivity association in over 100 coronary artery disease patients (York, et al., 2007). They measured symptoms of depression and reactivity during a public speaking stress task. Again, higher depressive symptom scores were associated with lower, not higher, reactivity. This direction of association has also recently been replicated in the Dutch Famine Cohort Study (de Rooij, Schene, Phillips, & Roseboom, 2010). Thus, it would appear that as putative risk factors for cardiovascular pathology, high levels of depressive symptomatology and exaggerated cardiovascular reactions to stress may operate independently of one another. More recently, it has also been shown that individuals with sub-clinical depression levels displayed blunted cardiovascular responses to tasks associated with the consequences of punishment and reward in comparison to those with higher depression scores (Brinkmann, Schupbach, Joye, & Gendolla, 2009). Similarly, depression is also characterised by diminished emotional responsiveness to pleasant stimuli and reward (Bylsma, Morris, & Rottenberg, 2008). For example, in a recent study depressed patients exhibited blunted emotional reactions to anticipated reward relative to controls, but did not differ from controls in their emotional responsiveness to anticipated punishment (McFarland & Klein, 2009). This also begs the question, answerable only by prospective designs, of whether low reactivity could be a risk marker for depression, and in the present article we present novel preliminary evidence that this is the case; lower HR reactivity was significantly related to an increase in depressive symptoms over the subsequent five years.

Obesity

The cross-sectional and prospective analyses of the associations among reactivity and body mass index and obesity show that, contrary to expectations based on the indicative rather than definitive outcomes of the few previous small scale studies, low cardiac reactivity was associated with a greater body mass index and greater likelihood of being obese. In addition, in prospective analyses low cardiac reactivity was associated with an increased risk of becoming obese in the subsequent five years. Again, these outcomes withstood adjustment for a range of socio-demographic factors and medication status. There is some other evidence that whereas the obese have elevated sympathetic tone in the resting state (Tentolouris, Liatis, & Katsilambros, 2006), their sympathetic nervous system may be less responsive

to stimulation. For example, after ingestion of a meal, there is a postprandial sympathetic nervous system response as reflected by higher plasma norepinephrine concentrations and an increased low- to high-frequency ratio in the heart rate variability spectrum (Tentolouris, Tsigos, Perea, Koukou, Kyriaki, Kitsou, Daskas, Daifotis, Makrilakis, Raptis, & Katsilambros, 2003; Welle, Lilavivat, & Campbell, 1981). However, this effect has been observed to be much smaller in obese as opposed to lean individuals (Tentolouris, et al., 2003). Further, the present findings do not appear to be driven by higher resting cardiovascular levels among obese individuals resulting in a ceiling effect on reactivity, given that these associations remained significant following adjustment for baseline cardiovascular levels. Additional support can be found in the observation that changes in heart rate and muscle sympathetic nerve stimulation after the infusion of antihypertensive and antihypotensive drugs were found to be significantly smaller in the obese than the non-obese (Grassi, Seravalle, Cattaneo, Bolla, Lanfranchi, Colombo, Giannattasio, Brunani, Cavagnini, & Mancia, 1995). Further, obesity is associated with a state of leptin resistance in humans, and hyperleptinaemia is related to lower sympathetic nervous system activity in obese individuals (Quilliot, Bohme, Zannad, & Ziegler, 2008), whereas circulating leptin has been shown to relate to acute stress-induced increases in heart rate in non-obese humans (Brydon, O'Donnell, Wright, Wawrzyniak, Wardle, & Steptoe, 2008). Thus, it is possible that obese individuals become resistant to the sympatho-activating effects of leptin, resulting in blunted reactivity. An alternative explanation for the associations between reactivity and obesity found here might be that individuals with obesity display a shift to peripheral vascular rather than cardiac responses to stress over time, thus resulting in blunted heart rate reactivity (Guyton & Hall, 2011). One mechanism for this might be via the abundance of cortisol receptors in the abdominal area noted in abdominal obesity, thus having a permissive effect on norepinephrine and exaggerating the vascular response to stress (Bjorntorp, 1991). However, it remains a possibility that low cardiac reactivity, by reflecting generally blunted sympathetic nervous system response to acute challenge, may be a risk marker for developing obesity.

Concluding remarks

There are a few factors to address when considering the consensus regarding blunted or lower reactivity emerging from this synthesis of analyses from the West of Scotland Twenty-07 study. First, and naturally, the consensus of findings should be treated with caution, given that they are emerging from the same dataset. However, the Study's principle aim was to investigate the processes that generate and maintain socio-demographic differences in health (Macintyre, 1987), thus participants

were chosen randomly with probability proportional to the overall population of the same age within a zip code area (Ecob, 1987). This careful match between the sample and general population makes us confident about our ability to generalise to the population at large. Further, the number of potential confounders our results withstood adjustment for, and the more recent emergence of some replicative and supportive data, discussed above, suggests that these findings are trustworthy, robust, replicable, and not simply a phenomenon of this particular study. In addition, the confirmation from other studies lend support to these findings of blunted reactivity. Second, the effect sizes for the results presented above were small by conventional standards. This, though, was our *a priori* expectation based on previous research and reinforces the value of large samples when examining some of the more subtle correlates of cardiovascular reactivity. Our effects are also of the same order as the positive associations between cardiovascular reactivity and future blood pressure status in this sample (Carroll, et al., 2003) and others (e.g. (Carroll, et al., 1995; Carroll, et al., 2001; Markovitz, et al., 1998)). In addition, these effect sizes in the categorical analyses are similar to, for example, those linking BMI, as a categorical variable, and future coronary heart disease risk (see e.g., (Bogers, et al., 2007)), which is considered to be a clinically significant association. Third, we measured only blood pressure and HR. It could have proved instructive to have the sort of comprehensive assessment of haemodynamics afforded by impedance cardiography or Finapres technology. However, the decision to use nurses to test participants in their own homes and the size of the sample precluded the use of impedance cardiography or Finapres in the Twenty-07 study. Further, many of the large scale epidemiological studies of reactivity have used averaged blood pressure and heart rate data in a similar way to the present study, see e.g., (Carroll et al., 1995; Lynch et al., 1998; Markovitz et al., 1998; Matthews et al., 2006). In addition, we did not have a detailed breakdown of the exact anti-hypertensive medications being taken by the sample, which may affect blood pressure and heart rate differently. However, we are confident that the adjustment for both medication usage in the 8.6% taking anti-hypertensives, and for baseline cardiovascular levels which different drugs may alter, should adequately take any such variation into account. Finally, it should be acknowledged that blunted heart rate reactivity may indicate a shift from cardiac stress responses towards more vascular responses, which were not measured in this study. However, that our findings for low reactivity emerged sometimes also for blunted blood pressure reactivity for some outcomes, suggests that blunted reactions do not necessarily reflect a shift from cardiac to peripheral vascular responses.

It would appear that hypertension and other cardiovascular disease manifestations aside, high cardiovascular reactivity may not always be associated with negative health outcomes and behaviours. The present research presents preliminary evidence that low reactivity may characterise those with more symptoms of depression and those who are fatter. Whereas the cardiovascular health consequences of excessive cardiovascular reactivity constitute a coherent whole, it is difficult to see what unites these apparently diverse corollaries of blunted reactivity. Depression and obesity are both characterised, to an extent, by behavioural expressions of disordered motivation towards food in obese individuals (Stice, Spoor, Bohon, & Small, 2008), and toward pleasant stimuli (Bylsma, et al., 2008) and reward (McFarland & Klein, 2009) among those with depression. Dependencies are also considered to be thus characterised (Lovallo, 2006). Therefore, it is possible that blunted reactivity may be a physiological marker of such motivational dysregulation. However, this is speculation, and further research is needed to confirm it; the neural correlates and mechanisms of such processes are discussed in more depth elsewhere (Lovallo, in press). The challenge for the future is to understand the neural processes that may be common to different behavioural patterns and dependencies, as well as their influence on physiological reactions to psychological stress.

In a recent meta-analysis, other negative psychological or behavioural traits, including anxiety, neuroticism, and negative affectivity, were also revealed to be related to decreased cardiovascular reactivity (Chida & Hamer, 2008). Although the mechanisms of such associations are not yet fully understood, the growing literature associated with low cardiovascular reactivity suggests that we need a new perspective on reactivity and an expanded conceptual model of how departures in either direction from normal physiological response patterns have implications for adverse health outcomes. A suggestion of how blunted as well as exaggerated reactivity may relate to different health outcomes is presented in Figure 2. Blunted, as well as exaggerated, reactivity may be non-adaptive and bad for our health.

[Insert Figure 2 about here]

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Table 1 Mean (SD) SBP, DBP, and HR baseline and reactivity by age cohort, sex, and occupational status

	SBP		DBP		HR	
	Baseline	Reactivity	Baseline	Reactivity	Baseline	Reactivity
Age Cohort:						
Youngest (N = 592)	120.0 (15.07)	10.1 (10.24)	73.4 (10.08)	6.8 (9.04)	67.5 (11.00)	10.0 (10.56)
Middle (N = 624)	127.1 (18.08)	12.3 (11.44)	80.6 (11.13)	7.1 (8.03)	66.7 (11.17)	7.7 (10.00)
Eldest (N = 431)	144.4 (21.68)	12.3 (13.92)	83.8 (11.17)	7.0 (8.92)	65.7 (9.92)	6.1 (7.74)
Sex:						
Male (N = 757)	134.7 (18.25)	12.8 (11.77)	81.2 (11.18)	7.2 (8.43)	64.7 (10.43)	8.7 (9.73)
Female (N = 890)	124.3 (21.07)	10.4 (11.70)	76.8 (11.56)	6.8 (8.81)	68.4 (10.84)	7.6 (9.83)
Occupational Group:						
Manual (N = 772)	130.5 (21.44)	11.1 (12.22)	79.3 (11.93)	6.5 (9.07)	67.0 (11.26)	6.9 (9.54)
Non-manual (N = 872)	127.8 (19.58)	11.8 (11.39)	78.4 (11.29)	7.3 (8.24)	66.5 (10.40)	9.1 (9.90)

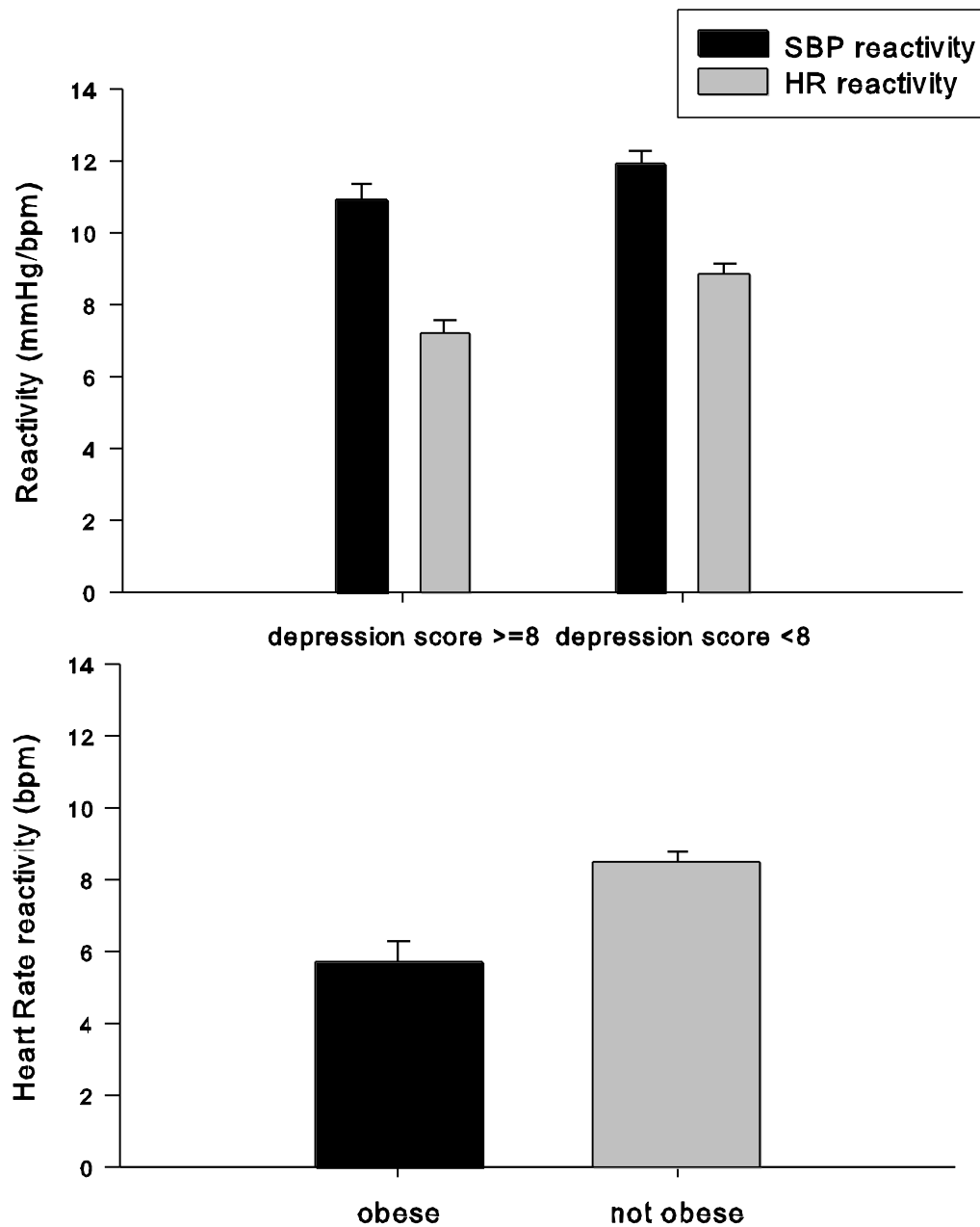


Figure 1 Cross-sectional fully adjusted associations between cardiovascular reactivity and depression score and obesity status.

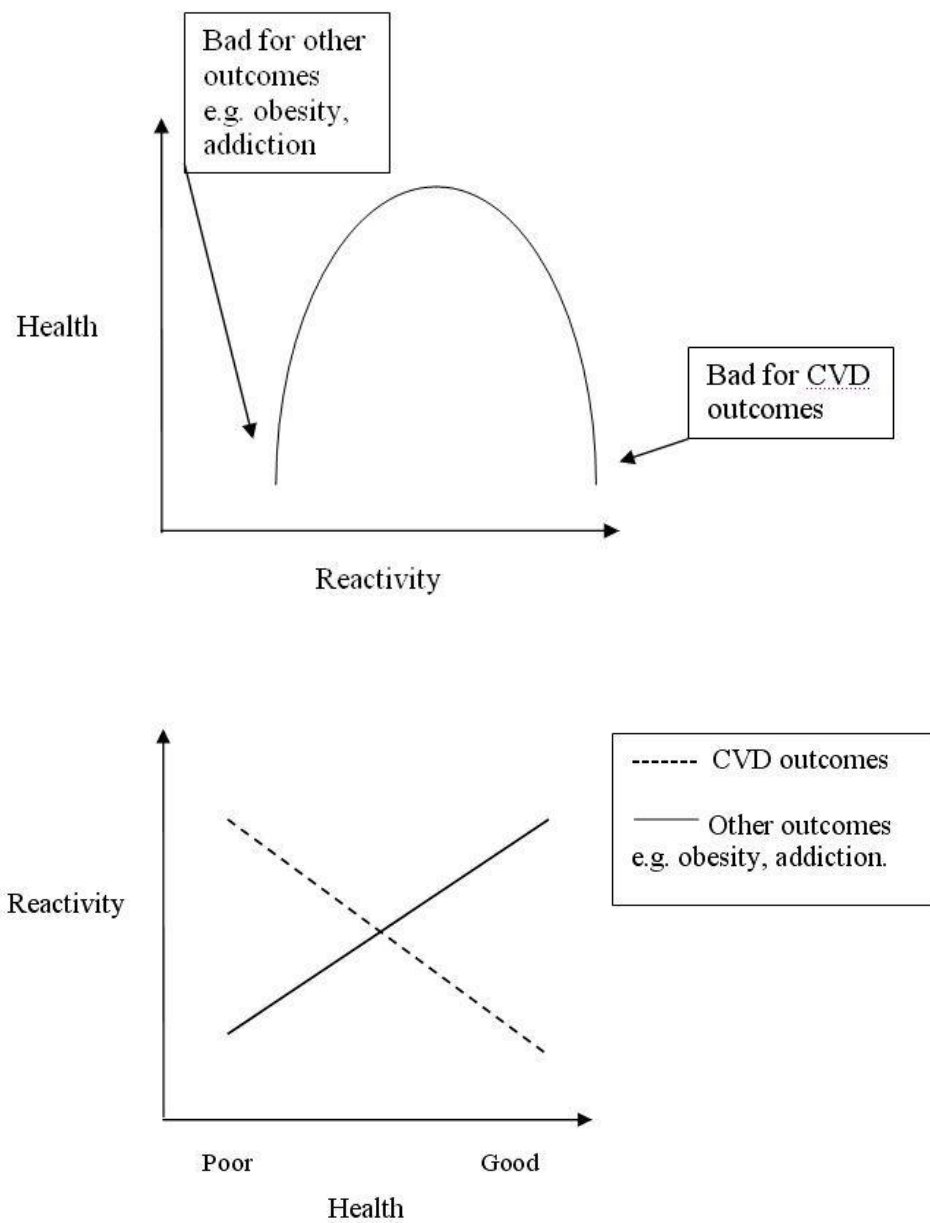


Figure 2 Potential models of how blunted as well as exaggerated reactivity might relate to health.